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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/656,356	09/05/2003	Samir M. Hanash	A31910-1	7827

38485 7590 10/24/2005

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EXAMINER	
NICKOL, GARY B	
ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 10/24/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/656,356	HANASH ET AL.	
	Examiner	Art Unit	
	Gary B. Nickol Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-26 is/are pending in the application.

4a) Of the above claim(s) 1-19 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 20-26 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Re: Hanash *et al.*

Date of priority: 08-06-1999

DETAILED ACTION

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-5, drawn to diagnosis and prognosis of cancer comprising detecting annexin protein in a biological sample, classified in class 435, subclass 7.23.

II. Claims 6-9, drawn to diagnosis of cancer comprising detecting autoantibodies specific for annexin, classified in class 424, subclass 9.1.

III. Claims 10-14, drawn to a kit comprising a component for detecting annexin protein wherein said component is an anti-annexin antibody, classified in class 435, subclass 810.

IV. Claims 15-19, drawn to a kit comprising a component for detecting annexin auto-antibodies wherein said component is annexin antigen, classified in class 435, subclass 810.

V. Claim 20-26, drawn to a method of immunizing a host against an annexin protein, classified in class 424, subclass 184.1.

The inventions are distinct, each from the other because of the following reasons:

The Inventions of Groups III-IV represent separate and distinct products which are made by materially different methods, and are used in materially different methods which have different modes of operation, different functions and different effects. For example, Group III is drawn to a kit comprising anti-annexin antibodies whereas the kit of Group IV comprises an annexin antigen. While the inventions of both Group III and Group IV are polypeptides, in this instance the polypeptides of Group III encompasses antibodies including IgG which comprises 2 heavy and 2 light chains containing constant and variable regions, and including framework regions which act as a scaffold for the 6 complementarily determining regions (CDR) that function to bind an epitope. Thus the polypeptides of Group IV and the antibodies of Group III are structurally distinct molecules; any relationship between a polypeptide of Group IV and an antibody of Group III is dependent upon the correlation between the scope of the polypeptides that the antibody binds and the scope of the antibodies that would be generated upon immunization with the polypeptide. In this case, the polypeptides of group IV encompass large molecules which contain potentially hundreds of regions to which an antibody may bind, whereas the antibody of Group III is defined in terms of its binding specificity to a small structure within the specific amino acid sequences. Furthermore, searching the inventions of Group IV and Group III would impose a serious search burden. The inventions have separate status in the art as shown by their different classifications. A polypeptide and an antibody which binds to the polypeptide require different searches.

The inventions of Groups I-II, and V are materially distinct methods that differ at least in objectives, method steps, reagents and/or dosages and/or schedules used, response variables, and

criteria for success. Group II requires the measurement of annexin auto-antibodies which is materally distinct from detecting the annexin antigen in Group I. Further, Group V encompasses methods of administering the annexin antigen which differs in method steps, dosages, and criteria for success compared to Groups I and II.

The inventions of Group III and the method of Group I are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (I) the process for using the product as claimed can be practiced with another materially different product or (ii) the product as claimed can be used in a materially different process of using that product [see *MPEP* § **806.05(h)**]. In the instant case the process for using the product can be practiced with annexin autoantibodies, a materially different product.

The invention of Group IV and the method of Group II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (I) the process for using the product as claimed can be practiced with another materially different product or (ii) the product as claimed can be used in a materially different process of using that product [see *MPEP* § **806.05(h)**]. In the instant case the annexin antigen as claimed can be used in a materially different process methods of immunizing a host.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, restriction for examination purposes as indicated is proper. Furthermore, because these inventions are distinct for the reasons given

above and the search required for one group is not required for another group, restriction for examination purposes as indicated is proper.

Note:

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product** will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.**

Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Telephone Election:

During a telephone conversation with Rochelle Seide on October 18, 2005 a provisional election was made with traverse to prosecute the invention of Group V, claims 20-26. *Affirmation of this election must be made by applicant in replying to this Office action.*

Claims 1-19 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Specification

The specification is objected to for the following reason: The specification on page 1 should be amended to reflect that the parent case (09/370, 337) has issued as US Patent No. **6645465.**

The specification is further objected to on page 9 as the brief description of Figures 4-6 lacks a representative description of subheadings 4A, 4B, 4C, 4D; 5A-5D, and 6A-6B.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 20 and 24 are rejected under 35 U.S.C. 102(b) as being anticipated by Seemann *et al.* Molecular Biology of the Cell. September 1996, Vol. 7, pages 1359-1374.

Seemann *et al.* teach (page 1362, 2nd column; Figure 3, page 1365) a method of immunizing a host against an annexin protein comprising inoculating the host with an Annexin I antigen wherein immunization results in a production of antibodies against Annexin I. Although the reference does not specifically teach the presence of a "physiologically acceptable carrier", the reference teaches that polyclonal Annexin I antibodies were raised in rabbits against purified Annexin I. Inherently, said Annexin I was formulated together with a physiologically acceptable carrier because such protocols are conventional in the art for producing polyclonal antibodies.

Claims 20 and 25 are rejected under 35 U.S.C. 102(b) as being anticipated by Hullin *et al.* (Jnl.Biol.Chem., February 1989,Vol. 264. No.6, pages 3506-3513).

Hullin *et al.* teach (page 3507, 2nd column) a method of immunizing a host against an annexin protein comprising subcutaneous injections of rabbits with Lipocortin II (also known as Annexin II) in a physiologically acceptable carrier (Freund adjuvant) wherein immunization results in a production of antibodies directed against Annexin II.

Claims 20 and 26 are rejected under 35 U.S.C. 102(b) as being anticipated by Sjolin *et al.* (Biochem. J., 1994, Vol. 300. Pages 325-330).

Sjolin *et al.* teach (page 326, 1st column) a method of immunizing a host against an annexin protein comprising inoculating the host with an annexin antigen wherein immunization results in a production of antibodies directed against said annexin antigen wherein the annexin protein is a modified protein. Specifically, Sjolin *et al.* teach the injection of rabbits with a peptide containing an annexin consensus sequence coupled to keyhole-limpet haemocyanin. Inherently, said peptide was formulated together with a physiologically acceptable carrier because such protocols are conventional in the art for producing polyclonal antibodies.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 20-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the immunization of host against an annexin protein where said immunization results in the production of antibodies, does not reasonably provide enablement for immunizing a host with an annexin protein wherein said host is suffering from cancer, including lung cancer for the purposes of immunotherapy. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *Ex parte* Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the

invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to a method of immunizing a host against an annexin protein or fragment thereof comprising inoculating the host with an annexin antigen wherein the host is suffering from a cancerous condition, such as lung cancer.

Thus, the claims, broadly encompass a method of treating cancer. Indeed, the specification teaches [para 12, see also para 54] that the invention relates to the use of annexin proteins as antigens to immunize patients suffering from diseases characterized by increased expression levels of the annexin protein antigens. The specification proposes that stimulation of an immunological response to such antigens is intended to elicit a more effective attack on tumor cells; such as inter alia inhibiting tumor cell growth or facilitating the killing of tumor cells.

However, the claims are not enabled because the specification lacks sufficient guidance and objective evidence for one of skill in the art to predictably treat cancer by the claimed method of immunizing a host with an annexin antigen. For example, the specification has not taught any dosage of antigen that would predictably elicit an effective immune response in a host that has cancer. Further the nature of the invention as well as the state of the art with regards to the immunotherapy of cancer is highly unpredictable.

For example, Bellone *et al.* . (Immunology Today, v20 (10), 1999, pp.457-462) summarize the current state of the art of peptide immunotherapy including clinical trials where "there is usually a poor correlation between induction of specific T-cells and the clinical

responses" (page 457, 2nd column). Bellone *et al.* teach the disadvantages of peptide cancer immunotherapy in that (1) there is no direct evidence for a role in tumor rejection, (2) the therapy is applicable to few patients, (3) risk of generating tumor escape mutants, and (4) risk of autoimmune reactions (page 461, Box 1). For example, Gaiger *et al.* (Blood, Volume 96, No. 4, August 2000, pages 1480-1489) chose to evaluate the Wilm's tumor antigen (WT1) as a potential immunotherapeutic as it is well known in the art that WT1 protein expression is more abundant in leukemia cells than in normal hematopoietic ells. However, WT1 peptide immunization did not show any effect on tumor growth in-vivo (Figure 10, page 1486). Further, Bodey *et al.* (Anticancer Research. 2000, Vol. 20, pages 2665-2676) teach that peptide vaccination against tumor antigens can induce powerful systemic CTL responses. However, in the majority of patients, no tumor regression is noted (page 2673, 1st column). The reference further teaches that active specific immunotherapy is still in its scientific infancy despite several decades of clinical and basic research. Even with some of the advances in melanoma cancer vaccines, their clinical effectiveness is "unclear" and adequately controlled studies have yet to be performed (page 2668, 2nd column). All of this underscores the criticality of providing some type of workable example, which is not disclosed in the specification, particularly in an unpredictable art, such as cancer therapy.

In view of the teachings above, and the lack of guidance and or exemplification in the specification, it would not be predictable for of skill in the art to practice the invention as broadly claimed. Thus, it would require undue experimentation by one of skill in the art to practice the invention as claimed.

Claims 20 and 24-26 are further rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention. The limitation of "inoculating a host" with an annexin antigen in a "physiologically acceptable carrier" has no clear support in the specification and the claims as originally filed. The specification only appears to contemplate "the use of annexin proteins as antigens to immunize patients suffering from diseases characterized by increased expression levels of the annexin protein antigens". Hence, there is no apparent nexus or contemplation for the mere immunization of a host for the purposes of producing antibodies. Applicant is required to cancel the **new matter** in the response to this Office Action. Alternatively, applicant is invited to provide sufficient written support for the "limitation" indicated above. See MPEP 714.02 and 2163.06.

No claim is allowed.

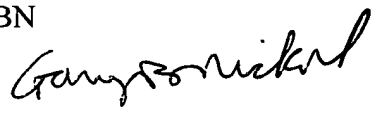
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary B. Nickol Ph.D. whose telephone number is 571-272-0835. The examiner can normally be reached on M-Th, 8:30-5:30; alternate Fri., 8:30-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gary B. Nickol Ph.D.
Primary Examiner
Art Unit 1642

GBN



GARY B. NICKOL, PH.D.
PRIMARY EXAMINER